

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074655

**Trade Name :RANITIDINE CAPSULES 150MG AND
300MG**

**Generic Name: Ranitidine Capsules 150mg and 300mg (as
the hydrochloride)**

Sponsor : Geneva Pharmaceuticals, Inc.

Approval Date: October 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074655

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **074655**

APPROVAL LETTER

31
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ANDA 74-655

OCT 30 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038-0446
|||||

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Capsules, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to our approval letter dated October 22, 1997.

This letter addresses issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to periods of patent protection which expire on June 4, 2002, (patent 4,521,431) and February 22, 2010 (patent 5,028,432). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Glaxo Wellcome Inc., Glaxo Group Limited and Allen and Hanbury's Limited v. Novartis Corporation, Geneva Pharmaceuticals Inc., Interchem Trading Corporation, and Union Quimico Farmaceutica S.A., Civil Action No. 94-1921, 94-4589 and 96-3849). You also have notified the Agency, that on October 1, 1997, the District Court hearing the patent case issued a Stipulated Dismissal pursuant to Rule 41(a)(1)(ii). This order states:

[T]he Dismissal will have the full force and effect of a decision of non-infringement of United States Patent Nos. 4,521,431, 4,128,658, 4,672,133 from which no appeal can be taken; and pursuant to 21 USC 355(j)(4)(B)(iii), the thirty (30) month stay of approval of Geneva Pharmaceutical Inc.'s ANDA 74-655 is dissolved and the Food and Drug Administration may approve ANDA 74-655 immediately.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Division of Bioequivalence has determined your Ranitidine Capsules, 150 mg(base) and 300 mg(base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac GELdose Capsules, 150 mg(base) and 300 mg(base), respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

10/22/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 22 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038-0446
|||||

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Capsules, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to your correspondence dated July 10, 1997, and to your amendments dated August 29 and October 1, 1997.

The listed drug product referenced in your application is subject to periods of patent protection which expire on June 4, 2002, (patent 4,521,431) and February 22, 2010 (patent 5,028,432). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Glaxo Wellcome Inc., Glaxo Group Limited and Allen and Hanbury's Limited v. Novartis Corporation, Geneva Pharmaceuticals Inc., Interchem Trading Corporation, and Union Quimico Farmaceutica S.A., Civil Action No. 94-1921, 94-4589 and 96-3849). You also have notified the Agency, that on October 1, 1997, the District Court hearing the patent case issued a Stipulated Dismissal pursuant to Rule 41(a)(1)(ii). This order states:

[T]he Dismissal will have the full force and effect of a decision of non-infringement of United States Patent Nos. 4,521,431, 4,128,658, 4,672,133 from which no appeal can be taken; and pursuant to 21 USC 355(j)(4)(B)(iii), the thirty (30) month stay of approval of Geneva Pharmaceutical Inc.'s ANDA 74-655 is dissolved and the Food and Drug Administration may approve ANDA 74-655 immediately.

The Agency has reviewed the application of the 180-day exclusivity provisions of the Act to this ANDA submitted for Ranitidine Capsules. FDA's regulations interpreting these provisions are set out at 21 CFR 314.107(c). The Agency has concluded that Geneva Pharmaceuticals is entitled to 180 days for marketing exclusivity for Ranitidine Capsules.

FDA regulations describe that the 180-day period will begin running from "the date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed." 21 CFR 314.107(c)(1)(ii). The relevant date of final decision of a court on patent issues is defined in 21 CFR 314.107(e)(2)(I) as follows:

If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.

As stated above, the right to appeal lapsed on October 1, 1997. The 180 day period began on October 1, 1997, and will expire on March 29, 1998. It is important to note that FDA will not approve an ANDA for ranitidine capsules prior to the expiration of exclusivity notwithstanding a licensing agreement.

If you have any questions concerning this matter, please feel free to contact Jerry Phillips; Director, Division of Labeling and Program Support at (301) 827-5846.

Sincerely yours,

10/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074655

FINAL PRINTED LABELING

Ranitidine Capsules
150 mg
CAUTION: Federal law prohibits dispensing without prescription.
30 CAPSULES

Geneva
pharmaceuticals, inc.



N 3 0781-2855-31 7
Each capsule contains: Ranitidine hydrochloride
USP equivalent to 150 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place.
Protect from light. Replace cap securely after opening. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 95-9M Manufactured By N9510
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT

EXP.

Ranitidine Capsules
150 mg
CAUTION: Federal law prohibits dispensing without prescription.
60 CAPSULES

Geneva
pharmaceuticals, inc.



N 3 0781-2855-60 7
Each capsule contains: Ranitidine hydrochloride,
USP equivalent to 150 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place.
Protect from light. Replace cap securely after opening. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 95-9M Manufactured By N9510
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT

EXP.

Ranitidine Capsules
150 mg
CAUTION: Federal law prohibits dispensing without prescription.
90 CAPSULES

Geneva
pharmaceuticals, inc.



N 3 0781-2855-92 8
Each capsule contains: Ranitidine hydrochloride
USP equivalent to 150 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place.
Protect from light. Replace cap securely after opening. KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 95-9M Manufactured By N9510
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT

EXP.

Ranitidine Capsules
300 mg

CAUTION: Federal law prohibits dispensing without prescription.
30 CAPSULES

Geneva
pharmaceuticals, inc.

N 3 0781-2865-31 6

Each capsule contains: Ranitidine hydrochloride USP equivalent to 300 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place. Protect from light. Replace cap securely after opening. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 95-9M Manufactured By N95/10
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:
EXP:

Ranitidine Capsules
300 mg

CAUTION: Federal law prohibits dispensing without prescription.
60 CAPSULES

Geneva
pharmaceuticals, inc.

N 3 0781-2865-60 6

Each capsule contains: Ranitidine hydrochloride USP equivalent to 300 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place. Protect from light. Replace cap securely after opening. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 95-9M Manufactured By N95/10
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:
EXP:

Ranitidine Capsules
300 mg

CAUTION: Federal law prohibits dispensing without prescription.
90 CAPSULES

Geneva
pharmaceuticals, inc.

N 3 0781-2865-92 7

Each capsule contains: Ranitidine hydrochloride. USP equivalent to 300 mg ranitidine.
Usual Dosage: See package insert.
Store between 20-25°C (36-77°F) in a dry place. Protect from light. Replace cap securely after opening. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 95-9M Manufactured By N95/10
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:
EXP:



Ranitidine Capsules

150 mg

CAUTION: Federal law prohibits dispensing
without prescription.

500 CAPSULES

Geneva
pharmaceuticals, inc.



N 0781-2855-05 8

Each capsule contains:

Ranitidine hydrochloride, USP equivalent to 150 mg ranitidine.

Usual Dosage: See package insert.

Store between 2°-25°C (36°-77°F) in a dry place. Protect from light.

Replace cap securely after opening.

Dispense in a tight, light-resistant container.

**KEEP THIS AND ALL DRUGS OUT OF THE REACH OF
CHILDREN.**

Rev. 97-3M

C97/4

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP:



Ranitidine Capsules

300 mg

CAUTION: Federal law prohibits dispensing
without prescription.

500 CAPSULES

Geneva
pharmaceuticals, inc.



N
3 0781-2865-05 7

Each capsule contains:

Ranitidine hydrochloride, USP equivalent to 300 mg ranitidine.

Usual Dosage: See package insert.

Store between 2°-25°C (36°-77°F) in a dry place. Protect from light.

Replace cap securely after opening.

Dispense in a tight, light-resistant container.

**KEEP THIS AND ALL DRUGS OUT OF THE REACH OF
CHILDREN.**

Rev. 97-3M

C97/4

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP:



7177

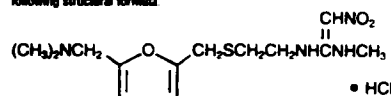
RANITIDINE CAPSULES

7177-4



DESCRIPTION: Ranitidine hydrochloride is a histamine H₂-receptor antagonist. Chemically it is N[2-[[[5-[[dimethylamino)methyl]-2-furanyl]methyl]thio]-ethyl]-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride.

Ranitidine HCl is a white to pale yellow, granular substance that is soluble in water. It has a slightly bitter taste and sulfur-like odor. It has the following structural formula:



• HCl

C₁₃H₂₂N₄O₃S • HCl

M.W. 350.87

Each capsule, for oral administration contains 168 mg or 336 mg ranitidine hydrochloride equivalent to 150 mg and 300 mg ranitidine, respectively. Inactive ingredients: Ammonium hydroxide, corn starch, FD & C Blue #1, FD & C Red #40, FD & C Yellow #6, gelatin, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, propylene glycol, silicon dioxide, simethicone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY: Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H₂-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca⁺⁺ in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. **Effects on Acid Secretion:** Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Effect of Oral Ranitidine on Gastric Acid Secretion

	Time after Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora — increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels — no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones — no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No endocrine action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics: Ranitidine is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150 mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Preprandial slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL per minute, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL per minute) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL per minute, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this

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In man, the N-acid is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-isomer (11%) and the desmethyl ranitidine (11%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study, of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in Table 1.

Table 1

	Ranitidine*		Placebo*	
	Number Entered	Healed/Evaluable	Number Entered	Healed/Evaluable
Outpatients				
Week 2	195	60/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†P < 0.0001.

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients as shown in Table 2.

Table 2

	Mean Daily Doses of Antacid	
	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg h.s.) than in patients treated with placebo over a 12-month period.

Duodenal Ulcer Prevalence

Double-blind, Multicenter, Placebo-controlled Trials

Multicenter Trial	Drug	Duodenal Ulcer Prevalence			No. of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN	20%*	24%*	35%*	138
	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	56%	64%	68%	165

% = Life-Table estimate.
* = P < 0.05 (Ranitidine versus comparator).
RAN = ranitidine.
PLC = placebo.

As with other H₂-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/Evaluable	Number Entered	Healed/Evaluable
Outpatients				
Week 2		16/83 (19%)		10/83 (12%)
Week 6	92	50/73 (68%)†	94	35/88 (51%)

* All patients were permitted p.r.n. antacids for relief of pain.
† P = 0.009.

In this multicenter trial, significantly more patients treated with ranitidine became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative "short-gut" syndrome, etc.). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect of heartburn extends through both the day and night time periods.

In two additional U.S. multicenter, double-blind, placebo-controlled, 12-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency and severity of heartburn.

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically-diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable			
	Placebo ^a n = 229		Ranitidine 150 mg q.i.d. ^a n = 215	
Week 4	43/198	(22%)	96/206	(47%)†
Week 8	63/176	(36%)	142/200	(71%)†
Week 12	92/159	(58%)	162/192	(84%)†

^a All patients were permitted p.r.n. antacids for relief of pain.
† p<0.001 versus placebo.
No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

- INDICATIONS AND USAGE:** Ranitidine capsules are indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
 2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
 3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
 4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
 5. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg b.i.d.
 6. Treatment of endoscopically-diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg q.i.d.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, GERD, and erosive esophagitis.

CONTRAINDICATIONS: Ranitidine is contraindicated in patients known to have hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS:

General:

1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.
2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.
3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ranitidine has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Cardiovascular, Metabolic, and Hematologic Effects: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (Salmonella, Escherichia coli) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation: Ranitidine is excreted in human milk. Caution should be exercised when ranitidine is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration. Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H₂-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, sinusoventric block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/burn, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or cholestatic, and/or cholestatic or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Immunohematologic: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and men have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and ranitidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been

war death.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocarcinoma or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Neuromuscular: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in women and men have shown no stimulation of any pituitary hormones by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme, and rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSEAGE: There has been limited experience with overdose. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdose occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD₅₀ values in mice and rats were 77 and 83 mg/kg, respectively.

DOSEAGE AND ADMINISTRATION:

Active Duodenal Ulcer: The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see CLINICAL PHARMACOLOGY: Clinical Trials).

Active Duodenal Ulcer: Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Ranitidine capsules, for oral administration, are supplied as:

150 mg: Opaque caramel capsules, imprinted GG 614 in white ink, filled with off-white powder in bottles of 30, 60, 90, and 500.

300 mg: Opaque caramel capsules, imprinted GG 615 in white ink, filled with off-white powder in bottles of 30, 60, 90, and 500.

Store between 20-25°C (36-77°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a light, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-3M

7177-4

C9714

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074655

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4a
2. ANDA # 74-655
3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446
4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine HCl Capsules, USP 150 mg and 300 mg are the generic version of the listed drug, Zantac®/Gel Dose 150 mg and 300 mg manufactured by Glaxo. Patent Nos. 4,128,658 and 4,521,431 which cover Polymorphic Form I and Form II respectively, will expire on 7/97 and on 2002. Also, patent No. 5,028,432 is referenced for the subject drug product which will expire on July 2, 2008. Paragraph III certifies that upon approval, the applicant will be able to make, use and sell the subject finished drug product as of December 5, 1995 (7/97 after GATT extension is applied).
5. SUPPLEMENT
N/A
6. PROPRIETARY NAME
7. NONPROPRIETARY NAME
Ranitidine Hydrochloride
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

March 31, 1995--	Original Submission
May 2, 1995--	Acknowledgment receipt
September 21, 1995--	Deficiency letter
January 22, 1996--	Bio. deficiency letter
February 5, 1996--	Amendment
May 10, 1996--	Bio letter
July 11, 1996--	Bio amendment
August 14, 1996--	Deficiency letter
January 16, 1997--	Amendment
January 23, 1997--	Bio review, acceptable.
March 14, 1997--	Deficiency letter (labeling)
March 25, 1997--	Amendment (labeling only)
July 10, 1997--	New Correspondence
July 24, 1997--	Tentative Approval
July 31, 1997--	Bio letter--acceptable
August 29, 1997--	Minor Amendment
October 1, 1997--	Minor Amendment
10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist
11. Rx or OTC
Rx
12. RELATED DMFs #

13. DOSAGE FORM
Capsules
14. POTENCY
150 mg & 300 mg
15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.
16. RECORDS AND REPORTS
N/A
17. COMMENTS

information can be found written in **bold** under each pertinent section of this review. No other changes are requested.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue. Patent litigation issues have been resolved due to a settlement agreement reached between the applicant and Glaxo.

19. REVIEWER:
Edwin Ramos
- DATE COMPLETED:
October 6, 1997

10/10/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074655

BIOEQUIVALENCE REVIEW(S)

AND A 74-655

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield 1 CO 80038-0446
|||||

JAN 29 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Capsule, 150 mg and 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following **tentative** specifications:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 23 1997

1

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655ADW.796

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
July 11, 1996

REVIEW OF A BIOEQUIVALENCE STUDY AMENDMENT, DISSOLUTION
TESTING, A WAIVER REQUEST, AND RECOMMENDATIONS FOR APPROVAL

Deficiency #1:

Response to Deficiency #1:

The firm's response is acceptable.

Deficiency #2:

Response to Deficiency #2:

The response is acceptable.

Deficiency #3:

Response to Deficiency #3:

The response is acceptable.

Deficiency #4:

Thirty-one (31) samples with code B (lost in process) were reanalyzed. The firm was requested to clarify how these samples were lost in process.

Response to Deficiency #4:

The firm has responded that

was used to

The samples coded 'lost in processing' were reassayed.

The firm's response is acceptable.

Deficiency #5:

The firm was requested to submit the SOP used for Analytical Method Validation

Response to Deficiency #5:

The firm has submitted the SOP used for the Analytical Method Validation.

The firm's response is acceptable.

Deficiency #6:

The dissolution of the test products were faster than the reference products. At 15 minutes, a mean of 96% and 99% were dissolved for the test products, 300 mg and 150 mg Capsules, respectively, compared with 58% and 67% for GELdose Capsules, 300 mg and 150 mg, respectively.

The firm was requested to submit comparative dissolution testings data conducted on 12 units of test and reference products in 900 mL water at 37° C, using both USP paddle at 50 RPM, and basket at 100 RPM. Sampling times of 10, 20, 30, and 45 minutes was recommended instead of 15, 30, 45, and 60 minutes.

Response to Deficiency #6:

The firm has submitted dissolution testings data conducted on 12 units of each the test, and reference products in 900 mL water at 37° C using apparatus 1 (basket) at 100 rpm, and apparatus 2 (paddle) at 50 rpm. The sampling times were at 10, 20, 30, and 45 minutes (Table 1). The proposed specifications are NLT at 45 minutes.

The dissolution data were similar using either paddle at 50 rpm, or basket at 100 rpm. Percent dissolved for the test and reference products were similar and above at 20, 30, and 45 minutes using either apparatus (Table 1). Percent dissolved at 10 minutes was higher for the test product compared with the reference product using either apparatus (Table 1).

Table 2 compares two different lots of the reference products,

lot #4B333 (300 mg) and lot #5M330 (300 mg). Lot #4B333, which was previously used for the bio-study and dissolution testing had been expired at the time of the new dissolution testing. The data show similarity between the two lots at all the times except for 20 minutes.

Table 2 also compares two different lots of the reference products, lot #4B356 (150 mg) and lot #6ZPC001 (150 mg). The data show similarity between the two lots at all the times.

The response is acceptable.

Deficiency #7:

The firm had requested a waiver of bioequivalence study for its test product, Ranitidine Capsules, 150 mg. However, the firm's bio-study for its 300 mg strength had been found incomplete. The firm has also requested a waiver in this submission.

Response to Deficiency #7:

The firm has responded to the bio-study deficiencies for its higher strength, 300 mg Capsules, and the study is acceptable. The dissolution testing conducted on both strengths are acceptable. The test products' compositions for 150 mg and 300 mg Capsules are proportionally similar (Table 3).

The response is acceptable.

COMMENT:

DEFICIENCY: None.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Capsules, 300 mg, lot #6494023, comparing it to Zantac Capsules, 300 mg, lot #4B333 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Geneva's ranitidine HCl, 300 mg Capsules is

manufactured by

2. The dissolution testing conducted by Geneva Pharmaceuticals on its Ranitidine HCl, 300 mg Capsules, lot #6494023 is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following **tentative** specifications:

Not less than of the labeled amount of the drug
in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalency and in vitro dissolution testing, and the application is acceptable.

5. The dissolution testing conducted by Geneva Pharmaceuticals on its drug, 150 mg Ranitidine HCl Capsules, lot #6494022 is acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 300 mg Capsules of the test product with 300 mg Capsules of the reference product Zantac manufactured by Glaxo Pharmaceuticals. The formulation of the 150 mg strength is proportionally similar to the 300 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 150 mg Capsules of the test product is granted. The 150 mg Capsules of the test product is therefore deemed bioequivalent to the 150 mg Capsules of Zantac manufactured by Glaxo Pharmaceuticals.

6. The firm should be informed of the COMMENT.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

12/4/96

Concur: _____

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 12/27/96

FNouravarsani/12-01-96/74655ADW.796

CC: ANDA #74-655 (Original, duplicate), Nouravarsani, HFD-658,
Drug File, Division File.

C: Paddle at 50 rpm, 150 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494022 Strength (mg) <u>150</u>	Reference Product Lot # 4B356 Strength (mg) <u>150</u>
	Mean% Range% (CV%)	Mean% Range% (CV%)
<u>10</u>	<u>59.0</u> (23.2)	<u>3.0</u> (60.0)
<u>20</u>	<u>96.0</u> (4.9)	<u>94.0</u> (6.8)
<u>30</u>	<u>100.0</u> (2.1)	<u>101.0</u> (2.3)
<u>45</u>	<u>100.0</u> (2.5)	<u>101.0</u> (1.8)

D: Basket at 100 rpm, 150 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494022 Strength (mg) <u>150</u>	Reference Product Lot # 4B356 Strength (mg) <u>150</u>
	Mean% Range% (CV%)	Mean% Range% (CV%)
<u>10</u>	<u>49.0</u> (17.6)	<u>4.0</u> (30.0)
<u>20</u>	<u>93.0</u> (7.0)	<u>96.0</u> (9.0)
<u>30</u>	<u>99.0</u> (2.7)	<u>102.0</u> (3.1)
<u>45</u>	<u>100.0</u> (2.0)	<u>102.0</u> (2.0)

Table 2: Comparison of Two Lots of the Reference Product

A. Paddle at 50 rpm, 300 mg Capsule

Sampling Times Minutes	Reference Product Lot # 5M330 Strength (mg) <u>300</u>			Reference Product Lot # 4B333 Strength (mg) <u>300</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>10</u>	<u>6.0</u>		(41.7)	<u>4.0</u>		(55.0)
<u>20</u>	<u>74.0</u>		(14.1)	<u>94.0</u>		(6.9)
<u>30</u>	<u>100.0</u>		(2.4)	<u>100.0</u>		(2.8)
<u>45</u>	<u>101.0</u>		(1.7)	<u>101.0</u>		(3.0)

B. Basket at 100 rpm, 300 mg Capsules

Sampling Times Minutes	Reference Product Lot # 5M330 Strength (mg) <u>300</u>			Reference Product Lot # 4B333 Strength (mg) <u>300</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>10</u>	<u>7.0</u>		(101)	<u>5.0</u>		(96.0)
<u>20</u>	<u>69.0</u>		(12.2)	<u>96.0</u>		(5.0)
<u>30</u>	<u>93.0</u>		(3.8)	<u>99.0</u>		(3.6)
<u>45</u>	<u>99.0</u>		(1.4)	<u>99.0</u>		(3.3)

C: Paddle at 50 rpm, 150 mg Capsules

Sampling Times Minutes	Reference Product Lot # 6ZPC001 Strength (mg) <u>150</u>			Reference Product Lot # 4B356 Strength (mg) <u>150</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>10</u>	<u>4.0</u>		(52.5)	<u>3.0</u>		(60.0)
<u>20</u>	<u>94.0</u>		(4.9)	<u>94.0</u>		(6.8)
<u>30</u>	<u>101.0</u>		(1.9)	<u>101.0</u>		(2.3)
<u>45</u>	<u>102.0</u>		(1.5)	<u>101.0</u>		(1.8)

D: Basket at 100 rpm, 150 mg Capsules

Sampling Times Minutes	Reference Product Lot # 6ZPC001 Strength (mg) <u>150</u>			Reference Product Lot # 4B356 Strength (mg) <u>150</u>		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
<u>10</u>	<u>9.0</u>		(101)	<u>4.0</u>		(30.0)
<u>20</u>	<u>96.0</u>		(5.3)	<u>96.0</u>		(9.0)
<u>30</u>	<u>101.0</u>		(2.5)	<u>102.0</u>		(3.1)
<u>45</u>	<u>102.0</u>		(2.5)	<u>102.0</u>		(2.0)

Table 3:Formulation Comparison:

<u>Ingredients</u>	<u>150 mg Capsule</u>	<u>300 mg Capsule</u>
Ranitidine HCl, USP	167.395 mg(a)	334.790 mg(b)
Microcrystalline Cellulose, NF		
Hydroxypropyl Methylcellulose USP		
Sodium Starch Glycolate, NF		
SD- Alcohol		
Magnesium Stearate, NF		
#3 Opaque Caramel Cap and Body Imprinted GG 614 in White Ink		
#1 Opaque Caramel Cap and Body Imprinted GG 615 in White Ink		
Corn Starch, NF		
Total Capsule Weight	222.000 mg	428.000 mg

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

JUL 31 1997

Geneva Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

Dear Ms. Brannan:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Capsules, 150 mg and 300 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug in the dosage forms dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

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fr

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D J

JUL 28 1997

1

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655DA.697

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
June 27, 1997

REVIEW OF A DISSOLUTION TESTING AMMENDMENT

In the current submission the firm has made references to the communication from the Division of Bioequivalence dated January 29, 1997, and phone conversation between OGD Chemist and Geneva (June 25, 1997). The firm stated that: "Geneva commits to incorporating the following dissolution testing into the stability and quality control programs:"

Medium: water, 900 mL at 37° C
Apparatus: paddle (2)
Rotation Speed: 50 rpm
Specifications: NLT at 30 minutes

Comment:

The firm incorporates the specifications of "NLT in 30 minutes" recommended by the Division of Bioequivalence. The firm had previously proposed specifications of "NLT in 45 minutes".

Recommendation:

No further action is required by the firm.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

Concur: _____
fr Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

7/14/97
Date: 7/28/97

DEC 19 1995

010

1

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655SDW.395

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
March 31, 1995

REVIEW OF A BIOEQUIVALENCE STUDY, DISSOLUTION
TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has submitted a bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Capsules, 300 mg, and Zantac GELdose Capsules, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #20095-002, March 08, 1994) as the listed reference product.

Ranitidine Hydrochloride, a histamine H₂-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The administration of food or antacids does not show a significant effect on the absorption of the Zantac. It has been reported in one study that simultaneous administration of Zantac with a high potency antacid (150 m mol) reduced the absorption of Zantac in fasting subjects. The elimination half-life is reported to be 2.5 to 3 hours (PDR 49, 1995).

Zantac GELdose capsules, 150 and 300 mg are soft gelatin capsules in a nonaqueous matrix of synthetic coconut oil and synthetic triglycerides.

BIOEQUIVALENCE STUDY:

Objectives:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride Capsules, 300 mg and the reference product, Zantac GELdose Capsules, 300 mg, under fasting conditions.
2. Compare the in vitro dissolution testing conducted on the test and reference products.
3. Request a waiver of bioequivalence study requirements for Ranitidine Hydrochloride Capsules, 150 mg.

Sponsor: Geneva Pharmaceuticals, Inc., Broomfield, CO

Manufactured by: Geneva Pharmaceuticals, Inc.
Contract Facility:

Principal Investigator:

Treatments:

Treatment A (test Product): A single dose of Ranitidine Capsules, 300 mg, lot #6494023, expiration date: 8/96, actual batch size Capsules.

Treatment B (reference Product): A single dose of Zantac GELdose Capsules, 300 mg, lot #4B333, expiration date: 8/95

Study Design:

A single dose of treatment A and B were administered randomly to healthy volunteers in a two - way crossover study design (protocol/report

Clinical Study Dates:

Phase I: September 28, 1994

Phase II: October 5, 1994

Washout period: 7 days.

Subjects:

Twenty-six (26) healthy male volunteers were enrolled. Two subjects served as alternates. Twenty-five subjects completed the study. Subject #4 withdrew from the study before the period 2, for personal reasons. This subject, who was in sequence BA, was unintentionally replaced by alternate subject #25 in sequence AB, instead of subject #26, who was in sequence BA. Data from 24 subjects were used for statistical data analyses.

Subjects number 1, 2, 5, 7, 9, 11, 12, 14, 15, 17, 20, 21, and 25 received treatment A in period I. The rest of the volunteers (3, 4, 6, 8, 10, 13, 16, 18, 19, 22, 23, 24, and 26) were dosed treatment A in period II.

The Mean (CV%) and range of the subjects' age, weight, and height are summarized as following:

	<u>Mean (CV%)</u>	<u>Range</u>
Age	28.8 (27.7%) years	19 - 44 years
Weight	72.8 (8.4%) kg	64.7 - 85.9 kg
Height	174.8 (3.5%) cm	162 - 187 cm

Housing, Fasting, Food and Fluid Intake:

All volunteers were housed in the from 12 hours prior to the administration of the dose until after last blood sample collection at 24 hours. The subjects fasted overnight prior to the dosing until 5 hours after the dose. Standard meals were served at 5 and approximately 10 hours after the dose. Except for 240 mL taken with the dose, water was not allowed from 2 hours before the dose, until 5 hours after.

Blood Samples:

Blood samples were collected at predose, and at 0.33, 0.50, 0.67, 1.0, 1.33, 1.5, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours after the dose.

Analytical Procedures:

Data Analysis:

The data were analyzed using SAS - GLM procedure. The two one-sided t-test procedure (90% confidence intervals) was used to compare the least square means of ln-transformed parameters of AUC(0-t), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Medical Event:

The only non-serious, mild, and probably drug related medical event was headache, reported by subject #19.

Results:

The mean plasma concentrations of ranitidine are summarized in Table 1. Linear and semi-ln plots of the mean plasma concentrations of ranitidine versus time for both test and reference products are shown in Figures 1 and 2. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 4404.8 hr*ng/mL, is comparable with the AUC(0-T) of 4143.7 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 4438.5 hr*ng/mL, is comparable with the one obtained for the reference product, 4189.7 hr*ng/mL.

The C(Max) for the test product, 859.93 ng/mL, is comparable with the C(Max) of 775.88 ng/mL for the reference product.

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 99.3% and 98.9%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 107.5%, 107.1%, and 116.5%, respectively (Table 4).

There are no product, period ($p=0.05$) and sequence ($p=0.1$) effects observed for the above pharmacokinetic parameters using ln-transformed or un-transformed parameters.

The 90% CIs calculated for the ln-transformed parameters fall in the required range of 80 - 125% (Table 2).

IN VITRO STUDIES:

Dissolution Testing:

Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Capsules, 300 mg (lot #6494023)

and the reference product, Zantac Capsules, 300 mg (lot #4B333) are shown in Table 5.

The dissolution testing was conducted in water at 37° C using USP XXII paddle at 50 RPM. The firm has proposed a specification of "Not less than _____ of the labeled amount dissolve in 45 minutes".

Not less than _____ (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes" for the test or reference product. The dissolution of no unit was less than Q - 15% at 45 minutes.

Results of the dissolution testing conducted on 12 units of the test product, 150 mg Capsules (lot #6494022) and reference product, 150 mg Zantac Capsules (lot #4B356) are shown in Table 5. Not less than _____ (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product. The dissolution of no unit was less than Q - 15% at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Capsules, 300 mg, and 150 mg were 100.9% (CV = 0.9%, N=10) and 99.1% (CV = 0.8%, N=10) of the labeled amount claimed, respectively. The assayed potencies of the reference products was reported as 99.6% (CV = 1.2%, N=3)) for the 300 mg capsules, and 100.1% (CV = 1.1%, N = 3) for 150 mg capsules.

Content Uniformity:

Values of 100.4% (CV = 1.5%, N=10) and 100.7% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount claimed for 10 Ranitidine HCl Capsules, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were 101.8% (CV = 1.8%, N=10) for 300 mg Capsules, and 99.8% (CV = 2.1%, N=10) for 150 mg Capsules.

Waiver Request for Ranitidine HCl Capsules, 150 mg:

The firm has requested a waiver of bioequivalence study requirements for its Ranitidine HCl Capsules, 150 mg based on similar formulations of the products (Table 6), dissolution testing for the 150 mg strength (Table 5), and in-vivo bio-study conducted on the 300 mg strength.

COMMENTS:

1. Lots #6494023 (test product) and #4B333 (reference product) were used for both the bioequivalence study and the dissolution testing. Theoretical batch size was _____ Capsules.

2. The 90% CIs calculated for the ln-transformed parameters fall in the required range of 80 - 125%.
3. No errors were found by spot checking of the calculations and statistical data analysis.
4. Multiple peaks are observed for both test and reference products in most of the subjects.
5. Sample at 0.5 hour, period 1, treatment B could not be collected for subject #13.
6. Plasma level could not be reported for subject #18, at 2.5 hour, period 2, test product due to insufficient sample volume for reanalysis.
7. Application Form FDA 356h was not included in the jacket.

DEFICIENCIES:

4. Thirty-one (31) samples with code B (lost in process) were

reanalyzed. The firm should clarify how these samples were lost in process.

5. The firm should submit the SOP used for Analytical Method Validation

6. The dissolution of the test products were faster than the reference products. At 15 minutes, a mean of 96% and 99% were dissolved for the test products, 300 mg and 150 mg Capsules, respectively, compared with 58% and 67% for GELdose Capsules, 300 mg and 150 mg, respectively.

The firm should submit comparative dissolution testings data conducted on 12 units of test and reference products in 900 mL water at 37° C, using both USP paddle at 50 RPM, and basket at 100 RPM. Sampling times of 10, 20, 30, and 45 minutes is recommended instead of 15, 30, 45, and 60 minutes.

RECOMMENDATION:

The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Capsules, 300 mg, lot #6494023, comparing it to Zantac Capsules, 300 mg, lot #4B333 has been found incomplete by the Division of Bioequivalence.

The firm should be informed of the DEFICIENCIES.

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRF

12/19/95

Concur:

Keith Chan, Ph.D.
Director
Division of Bioequivalence

Date: _____

FNouravarsani/11-22-95/74655SDW.395

CC: ANDA #74-655 (Original, duplicate), HFD-600 (Hare),
HFD-630, HFD-344 (CViswanathan), HFD-658
(Mhatre, Nouravarsani), Drug File, Division File.

Table 1:

Mean (CV%) Plasma Concentrations (ng/mL) of Ranitidine, N=24:

<u>Time, hr</u>	<u>Test Product</u>	<u>Reference Product</u>
0.00	0.000 (--)	0.000 (--)
0.33	48.96 (75)	21.38 (174)
0.50	174.52 (48)	132.09 (82)
0.67	289.27 (38)	242.70 (53)
1.00	373.19 (39)	356.73 (57)
1.33	408.71 (36)	412.00 (38)
1.50	404.25 (37)	420.79 (39)
1.67	426.14 (39)	441.84 (36)
2.00	586.32 (63)	517.12 (52)
2.50	700.89 (50)	560.57 (35)
3.00	693.40 (30)	583.26 (31)
3.50	684.50 (31)	586.17 (33)
4.00	645.08 (35)	564.33 (36)
5.00	518.73 (37)	497.79 (34)
6.00	400.08 (37)	390.78 (42)
8.00	210.07 (36)	212.71 (33)
10.00	113.86 (41)	121.01 (33)
12.00	65.33 (37)	69.38 (32)
16.00	23.09 (43)	26.56 (38)
24.00	6.16 (58)	7.64 (69)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI Obtained for 300 mg Capsules of the Test and Reference Products, N=24:

<u>Parameters</u>	<u>Test</u>	<u>Reference</u>	<u>90% CI (ln-trans.)</u>
AUC (0-T) hr*ng/mL	4404.8 (26.3)	4143.7 (21.2)	95.3 - 113.0
AUC (0-Inf) hr*ng/mL	4438.5 (26.4)	4189.7 (21.2)	95.1 - 112.6
C (Max) ng/mL	859.9 (39.4)	775.9 (32.7)	92.3 - 123.8
T (Max) hr	3.132 (29.8)	3.315 (39.0)	
K (Elm) 1/hr	0.218 (17.4)	0.210 (22.1)	
T (1/2) hr	3.26 (14.9)	3.50 (28.5)	

Table 3: AUC(0-T)/AUC(0-Inf) Percentage, N=24:

<u>Subject</u>	<u>Test</u>	<u>Reference</u>
01		
02		
03		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
Mean%	99.25	98.93
CV%	0.3	1.1
Range%	98.5% - 99.6%	94.6% - 99.7%

Table 4: Ratio Analysis of the Parameters, N=24:

<u>Subject</u>	<u>(Test/Reference) Percentage</u>		
	<u>AUC (0-T)</u>	<u>AUC (0-Inf)</u>	<u>C (Max)</u>
01			
02			
03			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
Mean%	107.50	107.06	116.47
CV%	22.5	22.1	37.2
Range%	46.6-145.4	46.7-144.9	30.3-213.9

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

Assay Methodology:

Proposed Specifications: NLT in 45 minutes

II. Results of In Vitro Dissolution Testing:

	Mean [±]	Range [±]	(CV%)	Mean [±]	Range [±]	(CV%)
<u>15</u>	<u>99.0</u>		(3.3)	<u>67.0</u>		(27.2)
<u>30</u>	<u>99.0</u>		(3.3)	<u>99.0</u>		(2.4)
<u>45</u>	<u>100.0</u>		(2.9)	<u>101.0</u>		(2.0)
<u>60</u>	<u>102.0</u>		(2.7)	<u>101.0</u>		(2.0)

Table 6:Formulation Comparison:

<u>Ingredients</u>	<u>150 mg Capsule</u>	<u>300 mg Capsule</u>
Ranitidine HCl, USP	167.395 mg(a)	334.790 mg(b)
Microcrystalline Cellulose, NF		
Hydroxypropyl Methylcellulose USP		
Sodium Starch Glycolate, NF		
SD Alcohol		
Magnesium Stearate, NF		
#3 Opaque Caramel Cap and Body Imprinted GG 614 in White Ink		
#1 Opaque Caramel Cap and Body Imprinted GG 615 in White Ink		
Corn Starch, NF		
Total Capsule Weight	222.000 mg	428.000 mg

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

Figure 1

**Mean Human Plasma Ranitidine Concentrations
(Linear Plot)**

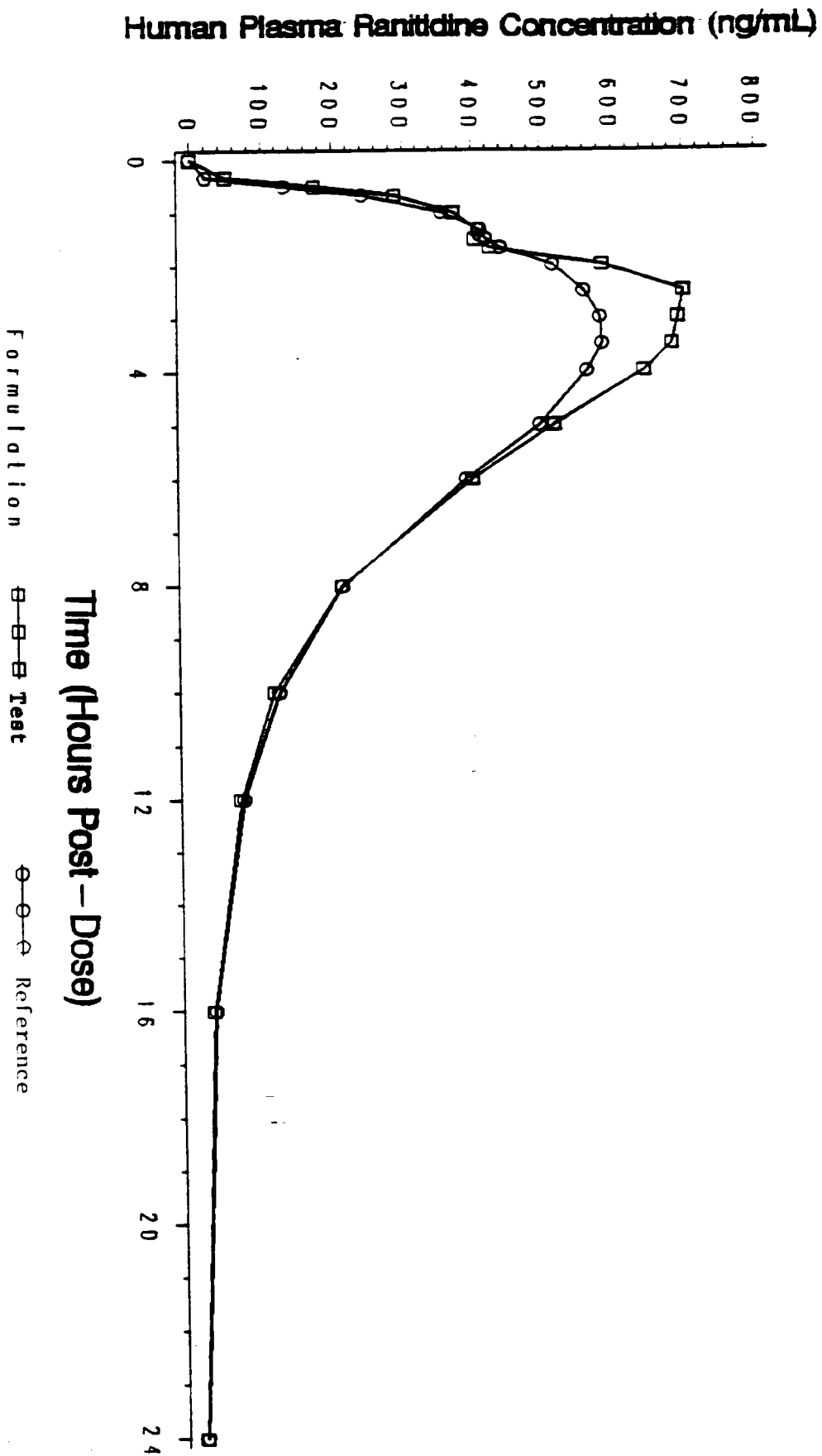


Figure 2

**Mean Human Plasma Ranitidine Concentrations
(Semi-Log Plot)**

